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(54) Title: SUPPLEMENTATION OF GLUCOCORTICOIDS

(57) Abstract

A formulation for and a method of treatment of dermatological conditions comprising the application of a formulation consisting of a glucocorticosteroid and a pharmaceutically acceptable zinc compound. The zinc compound may be zinc monoglycerolate.

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TITLE: SUPPLEMENTATION OF GLUCOCORTICOIDS

TECHNICAL FIELD

This invention relates to pharmaceutical formulations which enhance the pharmacological effect of topical corticosteroids for the treatment of dermatological conditions.

BACKGROUND ART

Glucocorticoids

The adrenal cortex synthesizes three classes of steroids: those with glucocorticoid actions, those with mineralocorticoid actions, and the sex corticoids which include mainly androgens. This invention is concerned with the steroids having glucocorticoid actions.

The pharmacological actions of the glucocorticosteroids are upon gluconeogenesis, glycogen deposition, and protein and calcium metabolism, together with inhibition of corticotrophin secretion, immunosuppression and anti-inflammatory activity. The naturally occurring glucocorticosteroids, principally hydrocortisone (endogenous hydrocortisone is often termed cortisol), are secreted by the adrenal cortex under the influence of the anterior pituitary corticotrophic hormone, corticotrophin, and they generally have both mineralocorticoid and glucocorticoid actions, the degree of these actions varying between the type of corticosteroid.

Many synthetic glucocorticosteroids have been produced with similar properties to the naturally occurring molecules. The aim in developing these synthetic analogues has usually been to produce enhanced potency. A second aim has been to synthesize compounds with increased glucocorticoid actions, but without a parallel increase in mineralocorticoid effect.

In the following discussion the term "glucocorticoids" refers to glucocorticosteroids.

Esterification of glucocorticoids at the 17 or 21 positions with fatty acids generally increases the activity on the skin. Some glucocorticoids esterified at the 17 position are much more potent topically than systemically, eg, beclomethasone dipropionate and betamethasone valerate.

Glucocorticoids affect protein metabolism: they have an anabolic effect, or increase the rate of synthesis, of proteins and RNA in liver; whereas they have catabolic effects in muscle, lymphoid tissue, adipose tissue, skin, and bone. Glucocorticoids act as immunosuppressants by suppressing protein synthesis, including synthesis of immunoglobulin. The also reduce populations of eosinophils, lymphocytes, and macrophages. Glucocorticoids are known to promote atrophy of lymphoid tissue in the thymus, spleen, and lymph nodes. Glucocorticoids inhibit the production of both interleukin-1 and macrophages, and interleukin-2 by helper T cells, thus decreasing T cell responses. The diminished helper T cells cause a decrease in B cells and antibody production.

The ability of glucocorticoids to suppress the inflammatory response is the basis for their major therapeutic uses. Glucocorticoids decrease the number of circulating lymphocytes, monocytes/macrophages, and eosinophils with these cells being relocated from the vascular compartment to other sites including the bone marrow, lymphoid tissue and spleen. Glucocorticoids inhibit the accumulation of leukocytes at the site of inflammation and inhibit the release from the leukocytes of substances involved in the inflammatory response (eg, kinins, plasminogen-activating factor, prostaglandins, and histamine). Glucocorticoids inhibit fibroblast proliferation and function at the site of an inflammatory response. This inhibition accounts for the poor wound healing, skin atrophy and increased susceptibility to infection that are often seen with patients with a glucocorticoid excess.

Glucocorticoids have been found to cause symptomatic improvement in a wide range of disease conditions, but it has been recognized at the same time that the glucocorticoids are not a cure for these diseases. It is therefore apparent that although glucocorticoids have a role in alleviating the symptoms of many disease conditions, they cause deficiencies or side effects that can, to a variable extent, counteract their alleviating role. These deficiencies or side effects include immunosuppression and increased susceptibility to infection, poor wound healing, skin atrophy, and decreased inflammatory response.

The various skin lesions caused by topical glucocorticoids differ from those observed after oral administration because the topically-applied drugs exert their actions in high concentrations at the application site.

Glucocorticoids cause another problem through a lowering of zinc levels in the human or animal body. Several studies in animals and humans have shown that zinc metabolism is significantly affected either by inflammation or by glucocorticoid administration (Fontaine J, Nève J, Peretz A, Capel P and Famaey JP, Agents and Actions 1991, 33:247-253). These drugs seem to induce synthesis of hepatic metallothionein, a powerful ligand for the element, causing accumulation of zinc in the liver with a resulting alteration in plasma levels. Oral long term treatment with corticosteroids as well as acute administration of intravenous high doses to rheumatoid arthritus patients caused significant decreases in plasma zinc levels (Peretz A, Nève J and Famaey J, J Trace Elem Electrolytes Health Dis 1989, 3:103-108; Flynn A, Strain WH, Pories WJ, Hill OA and Fratianne RB, Lancet 1971, ii: 1169-1171).

Zinc

Zinc is an essential trace element in all animals and plants, with vital roles in cellular structure and function, and as a component of over 300 enzymes. Zinc is essential for bone formation, tissue growth, cell-mediated immune function, host defence and wound repair. Homeostatic mechanisms control the level of zinc in the human or animal body, regulating the entry of zinc into, distribution in, and excretion from cells and tissues. Zinc can be absorbed percutaneously from topical application of some zinc compounds.

Zinc is an essential cofactor of DNA and RNA polymerase and is essential for cell division and RNA and protein synthesis. For this reason, relative zinc deficiencies seem to most significantly affect rapidly dividing cells or cells involved in protein synthesis. Major manifestations of zinc deficiency include a reduction in cell division leading to retarded growth and development, reproductive abnormalities, suppressed immunity, impaired wound healing, dermatitis, and impairments in neuropsychological functions. Low zinc levels are found when the body suffers from acute infection, inflammation, wounding, or physical or mental stress.

Zinc has a significant role in proper functioning of the immune system, as zinc

deficiency affects cell proliferation, protein synthesis, receptor activation, membrane activation, and cell migration, all of which influence the immune system. Zinc induces interferon-γ production, which in turn suppresses IgE synthesis through suppression of interleukin-4 synthesis. Zinc plays a central role in the activation and differentiation of T cells and natural killer cells, which are essential components of the cell-mediated immune system.

Zinc has been shown to influence the inflammatory process through stabilisation of the lysosomal membrane, inhibition of macrophage and neutrophil migration and phagocytic activity, inhibition of histamine release from mast cells, inhibition of prostaglandin synthesis, modulation of serotonin release from platelets, and modulation of lymphocyte proliferation.

Zinc has been found to have antibacterial activity. All living systems need zinc for growth, with bacteria generally requiring 10^{-10}M to 10^{-7}M for growth and 10^{-7}M to 10^{-5}M for optimal growth. At higher concentrations zinc inhibits cellular function: elevated concentrations of zinc may be inhibitory or toxic to cellular activities and growth of bacteria.

Zinc deficiency causes a depression of the rate of childhood growth, loss of hair, skin lesions, reproductive abnormalities, skeletal defects, impaired wound healing, and decreased immunocompetence.

In summary, it is apparent that glucocorticoids are very effective in reducing inflammation in a range of disease states, together with other symptoms of the diseases. At the same time there can be a reduction in immunocompetence, a reduction in healing rate of lesions or wounds, and a localized reduction of zinc tissue levels, particularly if the glucocorticoid is applied topically to intact or broken skin. This localized zinc deficiency can cause a further reduction in immunocompetence and a further decrease in the healing rate of lesions. It would therefore be an advantage if the localized zinc deficiency caused by a glucocorticoid could be overcome by an agent which corrects immunocompetence, increases healing rates, acts as an anti-inflammatory agent, and which also has antibacterial activity.

It is the object of this invention to provide a method of treatment of dermatological conditions or to at least provide an alternative treatment

process to those available at present.

DISCLOSURE OF THE INVENTION

In one form therefore the invention is said to reside in a method of treatment of dermatological conditions comprising the application of a formulation consisting of a glucocorticosteroid, a pharmaceutically acceptable zinc compound and a pharmaceutically acceptable carrier.

The formulation according to this invention provides substantial advantages over the use of glucocorticoids alone when glucocorticoids are applied topically to intact or broken skin. When provided through a suitable delivery vehicle, zinc has anti-inflammatory properties which enhance the effect of the glucocorticoid in this respect, and zinc can also provide an antibacterial effect. The presence of zinc is especially important in counteracting the negative aspects of glucocorticoid therapy: suppression of immunocompetence, reduction of healing rates, and atrophy of skin. Thus zinc enhances the immune function and it enhances healing rates of lesions and wounds.

Thus, in a further form the invention is said to reside in a method of treatment of dermatological conditions comprising the application of a formulation consisting of a glucocorticosteroid, a zinc compound and a pharmaceutically acceptable carrier, where the formulation is presented topically to intact skin or broken skin.

In a further form the invention is said to reside in a formulation for topical use consisting of a glucocorticosteroid, a pharmaceutically acceptable zinc compound and a pharmaceutically acceptable carrier, wherein the zinc compound is in a concentration of from 1 to 50%, and the glucocorticosteroid is at a concentration of 0.01 to 1%.

Topical glucocorticoids

Topical glucocorticoids are the treatment of choice in a number of dermatological conditions, including contact dermatitis, atopic dermatitis, nummular eczema, stasis eczema, lichen planus, lichen simplex chronicus, some burns and sunburns, and keloids. Topical glucocorticoids are useful as alternative or adjuvant treatments in psoriasis, seborrhoeic dermatitis, diaper

dermatitis (nappy rash), and a number of other miscellaneous dermatological disorders.

Clinical potencies of topical glucocorticoids are classed as mild (class I), moderately potent (class II), potent (class III), and very potent (class IV). Mild topical glucocorticoids include: aclomethasone dipropionate 0.05%, dexamethasone 0.01%, dexamethasone acetate 0.1%, hydrocortisone (alcohol or acetate) 0.1 to 1%, methylprednisolone acetate 0.25%, and prednisolone 0.5%. Moderately potent topical glucocorticoids include betamethasone valerate 0.02%, clobetasone butyrate 0.05%, flumethasone pivalate 0.02%, fluocinolone acetonide 0.01%, fluocortin butylester 0.75%, fluocortolone hexanoate 0.1%, fluocortolone pivalate 0.1 - 0.2%, fludroxycortide (flurandrenolone) 0.0125 to 0.025%, hydrocortisone 1% with urea, and triamcinolone acetonide 0.02%. Potent topical glucocorticoids include beclomethasone dipropionate 0.025%, betamethasone benzoate 0.025%, betamethasone dipropionate 0.05%, betamethasone valerate 0.05 to 0.1%, busonide 0.025%, desonide 0.05%, desoximethasone 0.25%, dexamethasone valerate 0.12%, diflorasone diacetate 0.05%, diflucortolone valerate 0.1%, fluclorolone acetonide 0.025%, fluocinolone acetonide 0.025%, fluocinonide 0.05%, fluocortolone hexanoate 0.25%, fluocortolone pivalate 0.25 to 0.5%, fluprednidene (fluprednylidene) acetate 0.1%, fludroxycortide (flurandrenolone) 0.05%, halcinonide 0.1%, hydrocortisone butyrate 0.1%, prednisolone valerate acetate 0.3%, and triamcinolone acetonide 0.05 to 0.1%. Very potent topical glucocorticoids include amcinonide 0.1%, beclomethasone dipropionate 0.5%, betamethasone dipropionate 0.5%, clobetasol propionate 0.05%, dexamethasone dipropionate 0.1%, diflorasone diacetate 0.05%, diflucortolone valerate 0.3%, difluprednate 0.05%, fluocinolone acetonide 0.2%, halcinonide 0.1%, hydrocortisone butyrate propionate 0.1%, ulobetasol (halobetasol) 0.05%, mometasone furoate 0.1%, and prednicarbate.

Zinc compounds

Zinc is widely available for oral administration to humans in the form of sulphate, acetate, acexamate, L-carnosine, gluconate and orotate salts, and a host of chelated complexes. During the past 20 years there has been a history of clinical studies where the efficacy of oral zinc supplementation for a range of disease conditions has been found to be positive, negative, or

inconclusive. It is believed that this lack of consistency, where the occurrence of spasmodic positive results indicates a positive effect of zinc, has been due to the limited delivery of zinc to the circulating plasma, as the absorption of zinc is dependent on the capacity of plasma to take up more zinc. Thus, rate of absorption, and the amount absorbed, will not only depend on the amount of the dose dissolved in the stomach contents, but it will also depend on the concentration of zinc in the blood stream at the time of dosing. Zinc supplementation, with the intention of increasing the transfer of zinc to specific tissue sites in the body, can therefore require special delivery systems or vehicles to distribute zinc to these tissues through pathways other than through the gastrointestinal tract.

Moreover, situations arise where intracellular zinc levels are suspected to be low due to symptomatic diagnosis but this localized zinc deficiency is not evident as the plasma zinc levels are normal. In these situations it would be preferable to deliver zinc to the zinc-deficient cells by topical administration, and at a controlled rate where the concentrations of zinc are not so high that toxicity occurs in other cells.

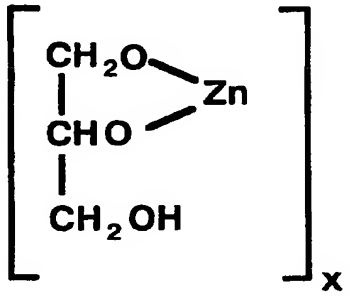
The zinc compound for use in the present invention may be selected from any physiologically acceptable zinc compound. This may include zinc acetate, zinc acexamate, zinc bacitracin, zinc caprylate, zinc carbonate, zinc L-carnosine, zinc chloride, zinc citrate, zinc lactate, zinc oleate, zinc orotate, zinc oxalate, zinc oxide, zinc permanganate, zinc *p*-phenolsulphate, zinc phosphate, zinc propionate, zinc salicylate, zinc stearate, zinc sulphate, zinc tartrate, and zinc valerate.

In further form therefore the invention is said to reside in a method of treatment of dermatological conditions comprising the application of a formulation consisting of a glucocorticosteroid selected from the group of compounds listed above and a zinc compound selected from the group of compounds listed above.

Zinc monoglycerolate

Another form of zinc compound which may be used in the formulation of the present invention is zinc monoglycerolate (ZMG or Glyzinc).

This relatively new form of zinc has been found to have advantageous physiological effects and is produced by mixing zinc oxide or a zinc oxide forming compound together with glycerol at temperatures sufficient for the reaction to proceed quantitatively to form zinc monoglycerolate which has the formula $(C_3H_6O_3Zn)_x$, with structure described by:



Zinc monoglycerolate is a white lubricious powder, the latter property being imparted by its polymeric two-dimensional structure. The compound is highly insoluble in water, but it is slowly soluble in a variety of biological fluids which imparts controlled release properties to the zinc (Fairlie, Whitehouse and Taylor, Agents Actions 1992; 36:152-158).

Zinc monoglycerolate has been shown to have special properties when applied topically as a powder or in a vehicle as it is readily absorbed into the skin, but it is not so effective when taken orally (Whitehouse, Rainsford, Taylor and Vernon-Roberts, Agents Actions 1990; 31:47-58). Poor oral absorption of zinc from zinc monoglycerolate can be attributed to a pH-dependent rate of hydrolysis of the compound by gastric acid, causing irregular and variable quantities of zinc ions to be available for absorption.

Studies with rats have shown that zinc monoglycerolate is an effective delivery system for zinc in the reduction of inflammation caused by adjuvant arthritis (Whitehouse, Rainsford, Taylor and Vernon-Roberts, Agents Actions 1990; 31:47-58). The animal studies indicated that zinc complexes given parenterally (dermally, intramuscularly, subcutaneously) are able to suppress chronic inflammation, while the same complexes given orally were virtually ineffective. The experimental observations collectively indicated that zinc monoglycerolate is a potent anti-inflammatory agent and is generally less toxic or irritant than other zinc complexes.

Zinc monoglycerolate has therefore been shown to be a useful delivery system for zinc in reducing chronic inflammation. Clinical studies in paediatric patients with mild to moderate atopic dermatitis have shown that zinc monoglycerolate is as effective as 1% hydrocortisone ointment in treating this disease. Zinc monoglycerolate has also been shown to be effective in the treatment of diaper dermatitis (nappy rash). Other studies have shown that zinc monoglycerolate is effective in enhancing healing of leg ulcers, pressure sores and burns. Zinc monoglycerolate therefore provides a useful delivery system for zinc in topical applications, both to intact skin and to open wounds.

The compound zinc monoglycerolate is preferred to other zinc compounds due to its structure which includes a three-carbon backbone providing a weak lipophilic property to the compound which assists in absorption of the zinc compound into tissues. Zinc monoglycerolate is innocuous from the aspect of toxicity as the products of hydrolysis are divalent zinc ions and glycerol. Zinc monoglycerolate also provides a slow release of zinc which is a distinct advantage when compared with soluble salts such as zinc sulphate or chloride which could be toxic to tissues in broken skin.

In further form therefore the invention is said to reside in a method of treatment of dermatological conditions comprising the application of a formulation consisting of a glucocorticosteroid selected from the group of compounds listed above and zinc monoglycerolate.

Administration

The mode of administration of the formulations may be similar to those currently used for the various disease states being treated. For example, treatment of dermatological conditions would be by an ointment when formulating zinc monoglycerolate with a glucocorticoid, as zinc monoglycerolate hydrolyzes in an aqueous environment. A cream could be used with a zinc compound that did not have this property of hydrolysis in aqueous media. Other forms of administration may include powder, liquid, suspension, gel, paste, wax or lotion.

In an ointment or cream formulation for topical use, the zinc compound may be included at a concentration of from 1 to 50%, and preferably 5 to 25%, the glucocorticoid being at a concentration in line with its potency, for example,

0.01 to 1%.

EXAMPLE 1

This example shows that the efficacy of topical zinc monoglycerolate is equivalent to that of 1% hydrocortisone ointment in treating atopic dermatitis in children. The study was a single-blind crossover evaluation of the efficacy and tolerance of zinc monoglycerolate and 1% hydrocortisone ointment in the treatment of childhood atopic dermatitis, carried out in four treatment centres. A total of 48 patients entered the study, of which 39 were evaluable. In the analysis of evaluable patients, Group 1 contained 17 patients and Group 2 contained 22 patients. The study design required a two-week initial washout with no treatment other than an emollient soap and emollient bath oil. A four-week treatment using one of the medications was followed by a two-week washout, before crossing over to the alternative medication. The results are best summarised by reference to the accompanying Figures in which:

Figure 1 shows a graph of Percentage Improvement in Mean Area Affected Scores plotted against weeks of treatment,

Figure 2 shows a graph of Percentage Improvement in Mean Skin Condition Scores plotted against weeks of treatment, and

Figure 3 shows a graph of Percentage Improvement in Mean Total Scores plotted against weeks of treatment, where Total Scores is the sum of the Area Affected Scores and Skin Condition Scores.

In Figure 1 for the Mean Area Affected Scores, zinc monoglycerolate and 1% hydrocortisone ointment were equally effective over the two study periods. Figure 2 for Mean Skin Condition Scores shows that the two preparations were equally effective over the first period, with hydrocortisone showing a non-significant improvement over zinc monoglycerolate in the second period. This difference in the second period may well have been due to a carry-over effect, where the prior treatment with zinc monoglycerolate provided an improved basis for continued treatment with hydrocortisone, in contrast to the other treatment schedule where hydrocortisone preceded zinc monoglycerolate.

Fig 3 shows the improvement in Mean Total Scores over the two treatment periods, where Total Scores is the sum of the Area Affected Scores and Skin Condition Scores. The improvement was equivalent for both zinc monoglycerolate and hydrocortisone for the first treatment period, with hydrocortisone showing a non-significant improvement over zinc monoglycerolate in the second period.

It can be seen that the improvement in the disease parameters was not complete within the study period as the plots had not levelled out.

EXAMPLE 2

A further example is currently being created. A study is to be conducted where 10% zinc monoglycerolate ointment is compared with 1% hydrocortisone ointment, and compared with 1% hydrocortisone ointment plus 10% zinc monoglycerolate ointment. This example will show the synergy of adding zinc monoglycerolate to hydrocortisone ointment, providing an increased effectiveness over hydrocortisone alone in treating atopic dermatitis. The study period will include 16 weeks of continuous treatment for each of the three formulations.

Throughout this specification and the claims that follow unless the context requires otherwise, the words 'comprise' and 'include' and variations such as 'comprising' and 'including' will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

CLAIMS

1/ A method of treatment of dermatological conditions comprising the application of a formulation consisting of a glucocorticosteroid, a pharmaceutically acceptable zinc compound and a pharmaceutically acceptable carrier.

2/ A method of treatment of dermatological conditions comprising the application of a formulation consisting of a glucocorticosteroid, a pharmaceutically acceptable zinc compound and a pharmaceutically acceptable carrier, where the formulation is presented topically to intact skin or to broken skin.

3/ A method of treatment as in Claim 1 or Claim 2 wherein the glucocorticosteroid is selected from the group comprising aclomethasone dipropionate, amcinonide, beclomethasone dipropionate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, busonide, clobetasol propionate, clobetasone butyrate, desonide, desoximethasone, dexamethasone, dexamethasone acetate, dexamethasone dipropionate, dexamethasone valerate, diflorasone diacetate, diflucortolone valerate, difluprednate, fluclorolone acetonide, fludroxycortide (flurandrenolone), flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortin butylester, fluocortolone hexanoate, fluocortolone pivalate, fluprednidene (fluprednylidene) acetate, halcinonide, hydrocortisone (alcohol or acetate), hydrocortisone butyrate, hydrocortisone butyrate propionate, hydrocortisone with urea, methylprednisolone acetate, mometasone furoate, prednicarbate., prednisolone, prednisolone valerate acetate, triamcinolone acetonide and ulobetasol (halobetasol).

4/ A method of treatment as in Claim 1 or Claim 2 wherein the zinc compound is selected from the group comprising zinc acetate, zinc acexamate, zinc bacitracin, zinc caprylate, zinc carbonate, zinc L-carnosine, zinc chloride, zinc citrate, zinc lactate, zinc oleate, zinc orotate, zinc oxalate, zinc oxide, zinc permanganate, zinc p-phenolsulphate, zinc phosphate, zinc propionate, zinc salicylate, zinc stearate, zinc sulphate, zinc tartrate, and zinc valerate.

5/ A method of treatment as in Claim 1 or Claim 2 wherein the zinc compound is zinc monoglycerolate.

6/ A method of treatment of dermatological conditions comprising the application of a formulation consisting of a glucocorticosteroid and zinc monoglycerolate.

7/ A method of treatment of dermatological conditions as in any one previous claim wherein the mode of administration of the formulation is by an ointment, lotion, gel, stick, wax, paste, solution, dispersion, liquid or a cream.

8/ A method of treatment of dermatological conditions as in Claim 7 wherein in the formulation for topical use, the zinc compound is in a concentration of from 1 to 50%, and the glucocorticosteroid is at a concentration of 0.01 to 1%.

9/ A method of treatment of dermatological conditions as in Claim 7 wherein in the ointment or cream formulation for topical use, the zinc compound is in a concentration of from 5 to 25%.

10/ A formulation for topical use consisting of a glucocorticosteroid, a pharmaceutically acceptable zinc compound and a pharmaceutically acceptable carrier, wherein the zinc compound is in a concentration of from 1 to 50%, and the glucocorticosteroid is at a concentration of 0.01 to 1%.

11/ A formulation as in Claim 10 wherein the zinc compound is in a concentration of from 5 to 25%.

12/ A formulation as in Claim 10 wherein the glucocorticosteroid is selected from the group comprising aclomethasone dipropionate, amcinonide, beclomethasone dipropionate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, busonide, clobetasol propionate, clobetasone butyrate, desonide, desoximethasone, dexamethasone, dexamethasone acetate, dexamethasone dipropionate, dexamethasone valerate, diflorasone diacetate, diflucortolone valerate, difluprednate, fluclorolone acetonide, fludroxycortide (flurandrenolone), flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortin butylester, fluocortolone hexanoate, fluocortolone pivalate, fluprednidene (fluprednylidene) acetate, halcinonide, hydrocortisone (alcohol or acetate), hydrocortisone butyrate, hydrocortisone butyrate propionate, hydrocortisone with urea, methylprednisolone acetate, mometasone furoate, prednicarbate., prednisolone, prednisolone valerate acetate, triamcinolone acetonide and ulobetasol (halobetasol).

13/ A formulation as in Claim 10 wherein the zinc compound is selected from the group comprising zinc acetate, zinc acexamate, zinc bacitracin, zinc caprylate, zinc carbonate, zinc L-carnosine, zinc chloride, zinc citrate, zinc lactate, zinc oleate, zinc orotate, zinc oxalate, zinc oxide, zinc permanganate, zinc p-phenolsulphate, zinc phosphate, zinc propionate, zinc salicylate, zinc stearate, zinc sulphate, zinc tartrate, and zinc valerate.

14/ A formulation as in Claim 10 wherein the zinc compound is zinc monoglycerolate.

15/ A formulation for topical use consisting of a glucocorticosteroid, zinc monoglycerolate and a pharmaceutically acceptable carrier, wherein the zinc monoglycerolate is in a concentration of from 1 to 50%, and the glucocorticosteroid is at a concentration of 0.01 to 1%.

AMENDED CLAIMS

[received by the International Bureau on 12 May 1997 (12.05.97); original claims 4-6 and 13-15 cancelled; original claim 7 renumbered as claim 4; original claims 8-12 amended and renumbered as claims 5-9; remaining claims unchanged (2 pages)]

1. A method of treatment of dermatological conditions comprising the application of a formulation consisting of a glucocorticosteroid, zinc monoglycerolate and a pharmaceutically acceptable carrier.

2. A method of treatment of dermatological conditions comprising the application of a formulation consisting of a glucocorticosteroid, zinc monoglycerolate and a pharmaceutically acceptable carrier, where the formulation is presented topically to intact skin or to broken skin.

3. A method of treatment as in Claim 1 or Claim 2 wherein the glucocorticosteroid is selected from the group comprising aclomethasone dipropionate, amcinonide, beclomethasone dipropionate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, busonide, clobetasol propionate, clobetasone butyrate, desonide, desoximethasone, dexamethasone, dexamethasone acetate, dexamethasone dipropionate, dexamethasone valerate, diflorasone diacetate, diflucortolone valerate, difluprednate, fluclorolone acetonide, fludroxycortide (flurandrenolone), flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortin butylester, fluocortolone hexanoate, fluocortolone pivalate, fluprednidene (fluprednylidene) acetate, halcinonide, hydrocortisone (alcohol or acetate), hydrocortisone butyrate, hydrocortisone butyrate propionate, hydrocortisone with urea, methylprednisolone acetate, mometasone furoate, prednicarbate., prednisolone, prednisolone valerate acetate, triamcinolone acetonide and ulobetasol (halobetasol).

4. A method of treatment of dermatological conditions as in any one previous claim wherein the mode of administration of the formulation is by an ointment, lotion, gel, stick, wax, paste, solution, dispersion, liquid or a cream.

5. A method of treatment of dermatological conditions as in any one previous claim wherein in the formulation for topical use, the zinc monoglycerolate is in a concentration of from 1 to 50%, and the glucocorticosteroid is at a concentration of 0.01 to 1%.

6. A method of treatment of dermatological conditions as in any one previous claim wherein in the ointment or cream formulation for topical use, the zinc monoglycerolate is in a concentration of from 5 to 25%.

7. A formulation for topical use consisting of a glucocorticosteroid, zinc monoglycerolate and a pharmaceutically acceptable carrier, wherein the zinc monoglycerolate is in a concentration of from 1 to 50%, and the glucocorticosteroid is at a concentration of 0.01 to 1%.

8. A formulation as in Claim 7 wherein the zinc monoglycerolate is in a concentration of from 5 to 25%.

9. A formulation as in Claim 7 wherein the glucocorticosteroid is selected from the group comprising aclomethasone dipropionate, amcinonide, beclomethasone dipropionate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, busonide, clobetasol propionate, clobetasone butyrate, desonide, desoximethasone, dexamethasone, dexamethasone acetate, dexamethasone dipropionate, dexamethasone valerate, diflorasone diacetate, diflucortolone valerate, difluprednate, fluclorolone acetonide, fludroxycortide (flurandrenolone), flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortin butylester, fluocortolone hexanoate, fluocortolone pivalate, fluprednidene (fluprednylidene) acetate, halcinonide, hydrocortisone (alcohol or acetate), hydrocortisone butyrate, hydrocortisone butyrate propionate, hydrocortisone with urea, methylprednisolone acetate, mometasone furoate, prednicarbate., prednisolone, prednisolone valerate acetate, triamcinolone acetonide and ulobetasol (halobetasol).

FIGURE 1

Percentage Improvement in Mean Area Affected Scores

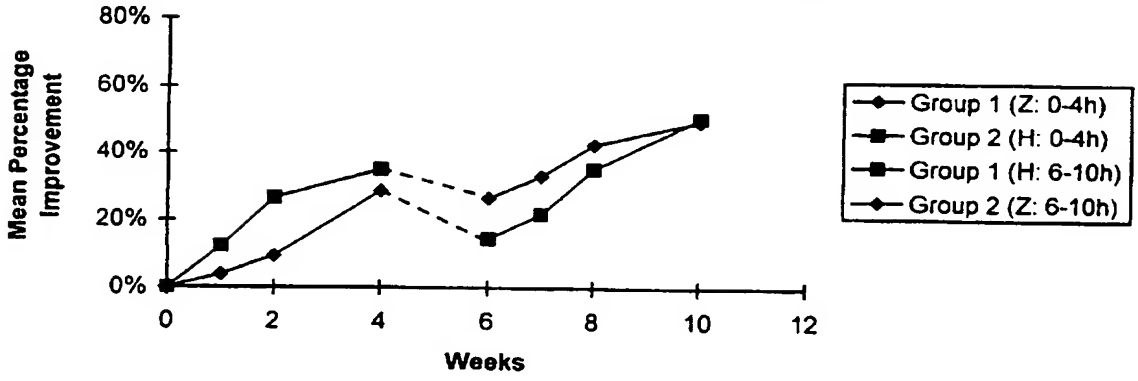


FIGURE 2

Percentage Improvement in Mean Skin Condition Scores

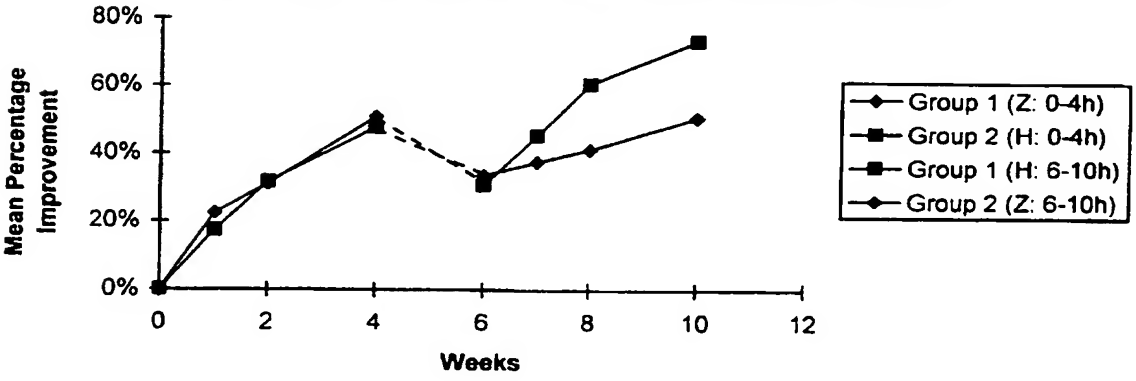
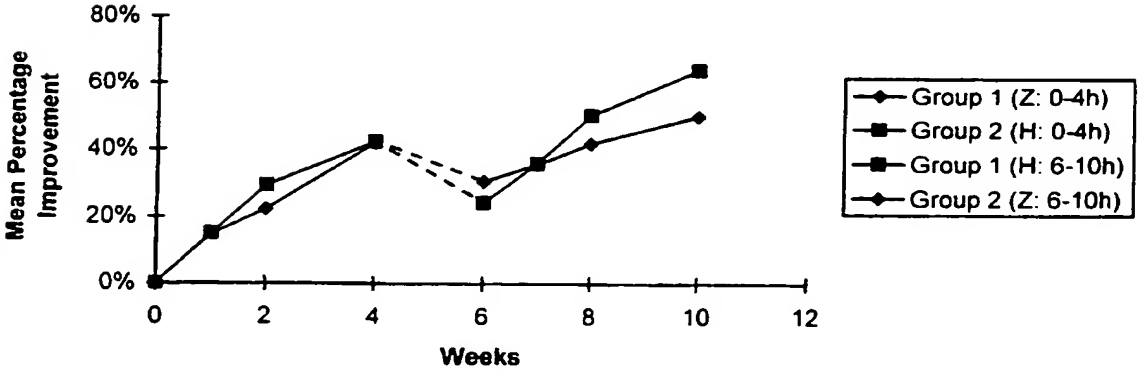


FIGURE 3

Percentage Improvement in Total Scores



INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 97/00048

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 33/30, 31/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61K 33/30, 31/57

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT WPAT, JAPIO; CHEMICAL ABSTRACTS CASM
Keywords: Glucocorticoster:, zinc; steriods listed in claims

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Derwent WPAT online Abstract no. 88-026753, class B04; RO 92445 (INTR. ANTIBIOTICE) 30 September 1987	1-15
X	Derwent WPAT online Abstract no. 91-213826, class A96; SU 1510131 (MOSC. MEDICINE INST. et al.)	10-15
X	Patent Abstracts of Japan, C 387, page 83 and JP 61-151121 A (TAISHO PHARM. CO. LTD.) 9 July 1986	10-15

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 MAR 1997	12.03.97
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (06) 285 3929	Authorized officer DAVID HENNESSY Telephone No.: (06) 283 2255

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 97/00048

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Derwent Abstract Accession no. 86-067649/10, class P31, SU 117400 A (CHITA MEDICINE INST.) 23 August 1985	10-15
X	ES 873891 A (LABORATORIES VINAS, S.A.) 16 May 1987. See the abstract, page 2, lines 20-24	10-15
X Y	AU 69664/94 A (GLYZINC PHARMECEUTICALS LIMITED) 22 December 1994. See page 11, line 28 to page 12, line 24	10-15 1-15
X	AU 16553/88 A (BIOGAL GYOGYSZERGYAR) 30 November 1989. See page 6, line 3; page 11, lines 22-25, claim 3	
X	US 4121940 A (Michel et al.) 24 October 1978. See column 1, lines 58-61	10-15
X	US 3255079 A (Schroeder et al.) 7 June 1966. See column 2, line 39 - column 3, line 40	10-15
X	Müller, Von R. et al. (1989) Reaktion und Wirksamkeit von Prednisolon in zinkoxidhaltigen Dermatika, Dermatol. Mon. Schr. 175, pages 82-86. See the discussion.	1-15
X,Y	Mullin, C.H. et al. (1987) Specific induction of Metallothionein in Hairless Mouse Skin by Zinc and Dexamethasone, Journal of Investigative Dermatology, volume 89 no.2, pages 164-166	1-15
X	Nakamura Masayuki (1975) Effects of Corticosteroids and Zinx on Wound Healing of Rat Skin, The Journal of Osaka University Dental Society, vol. 20 no. 2, pages 105-119. See whole document	1-15
X	Yoshida, A. et al. (1991) Basal studies on the mode of circular excision wounds made on the dorsal skin of rats treated with hydrocorticone, Folia pharmacol. Japon., vol. 98, pages 369-377. See whole document	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/AU 97/00048

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
AU	6966494	WO	9428884		
AU	1655388	EP	343268	CN	1038758
US	4121940	CA	1104058	JP	53133640

END OF ANNEX